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| 10/054,647 | 01/22/2002 | Robert Lawton | 00-1278-C | 9151 |

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| EXAMINER | |
|---|---|
| FORD, VANESSA L | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1645 | |

DATE MAILED: 05/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/054,647 | LAWTON ET AL. | |
| | Examiner | Art Unit | |
| | Vanessa L. Ford | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 February 2004* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## FINAL ACTION

1. This Office Action is responsive to Applicant's amendment and response filed February 23, 2004. Claims 1, 3, 5 and 7-9 have been amended. Clams 10-13 have been added. The Declaration filed under 37 C.F.R. 1.132 (declaration of Dr. Chandrashekar) is acknowledged but is insufficient to overcome the art rejection. Applicant's submission of Bowie et al *(Science 247:1306-1310 (1990))* is acknowledged.

2. The text of those sections of the Title 35, U.S. code not included in this action can be found in the prior Office Action.

### *Rejection Withdrawn*

3. In view of Applicant's amendment and response the following rejections are withdrawn:

a) rejection of claims 1-9 under 35 U.S.C. 112, second paragraph, page 12, paragraph 6.

b) rejection of claims 5 and 9 under 35 U.S.C. 112, second paragraph, page 12, paragraph 8.

***Rejections Maintained***

4. The rejection under 35 U.S.C. 112, first paragraph (written description) maintained for claims 1-9 and newly submitted claims 10-13 for the reasons set forth in pages 2-6 paragraph 3 of the previous Office Action.

The rejection was on the grounds that the claims are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. *This is a written description rejection.*

The specification broadly describes as a part of the invention a composition and an article of manufacture comprising the isolated polypeptide of SEQ ID No: 2 and variants thereof. The specification states "variants in which amino acids of the polypeptides of the invention are substituted, deleted or added in any combination are contemplated by the invention". The specification also states " that naturally occurring variants and non-naturally occurring variants are included in the invention and may be produced by mutagenesis techniques or by direct synthesis" (page 7). Applicant has broadly described the invention as embracing any substitution, insertion or deletion change of amino acids throughout the length of the polypeptide sequence. Variants of SEQ ID No:2 correspond to sequences from other species, mutated sequences, allelic variants, splice variants, sequences that have a variant degree of identity (similarity, homology), and so forth. None of these sequences meet the written description provision of 35 U.S.C. 112, first, paragraph. The specification provides insufficient written description to support the genus encompassed by the claim. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO:2, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptide regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, only SEQ ID NO: 2 but not the full breadth of the claim (or none of the sequences encompassed by the claim) meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicant urges that the standard under 112 first paragraph written description does not state that one skilled in the art must be able to determine amino acid substitution variants of SEQ ID NO:2 without looking or hunting for the variants. Applicant urges that written description does not require that the specific locations can be substituted or the specific structure be disclosed. Applicant urges that the standard for written description requires that one skilled in the art must recognize that the applicant was in possession of the claimed genus, that is, variants of SEQ ID NO:2. Applicant urges that one skilled in the art would recognize that Applicant was in possession of the genus in view of the species disclosed because the partial structure, physical and/or chemical properties, functional characteristics and methods of making the claimed variants is disclosed in the specification.

Applicant's arguments filed February 23, 2004 have been fully considered but they are not persuasive. It is the Examiner's position that there is nothing on the record to show that the specification is enabled for the full scope of the claims and therefore does not meet the written description requirement as set forth in 35 U.S.C. 112, first paragraph. Applicant has not shown enablement for variants of SEQ ID No.2. The specification discloses only species SEQ ID NO: 2 within the genus of the claimed invention. The specification proposes to discover other members of the genus by using

a sequence comparison algorithm (pages 6-7). The specification also states " that naturally occurring variants and non-naturally occurring variants are include in the invention and may be produced by mutagenesis techniques or by direct synthesis" (page 7). The specification discloses only SEQ ID NO:2 which corresponds to an isolated polypeptide of *Ehrlichia*. While use of BLAST and other sequence comparison tools are known, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the polypeptide's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any protein and the result of such modifications is unpredictable based on the instant disclosure. However, the claims are directed to a composition of matter consisting essentially of SEQ ID NO:2 or a phenotypically silent amino acid substitution variant thereof that specifically binds to an anti-*Ehrlichia* antibodies which encompasses sequences from other species, mutated sequences, splice variants, sequences that have a recited degree of identity (similarity, homology), and so forth. The general knowledge of the art concerning species does not provide any indication of how the structure of a limited number of other species is representative of unknown species. The nature of the species within a genus are variant structures. The requirement under the 35 U.S.C. 112, first written description is that the Applicant is in possession of the claimed invention. How can one of skilled in the art conclude that Applicant was in possession of the claimed invention if there is no structural description for a phenotypically silent amino acid substitution variant of SEQ ID NO:2? One skilled

in the art would concluded that Applicants were not in possession of the claimed genus polypeptides.

5. The rejection under 35 U.S.C. 112, first paragraph (enablement) is maintained for claims 1-9 and newly submitted claims 101-13 for the reasons set forth in pages 6-9, paragraph 4 of the previous Office Action.

The rejection was on the grounds that the claims rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition and an article of manufacture that comprise SEQ ID No:2, does not reasonably provide enablement for a composition or an article of manufacture that comprise variants of SEQ ID. No:2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-6 are directed to a composition and a article of manufacture comprising the isolated polypeptides of SEQ ID NO: 2 and variants thereof.

The specification is enabling only for the polypeptides of SEQ ID NO:2 as disclosed in the specification. The specification states that "variants in which amino acids of the polypeptides of the invention are substituted, deleted or added in any combination are contemplated by the invention". The specification also states " that naturally occurring variants and non-naturally occurring variants are included in the invention and may be produced by mutagenesis techniques or by direct synthesis" (page 7). The specification teaches that there are many tolerable and conservative amino acid substitutions which can be made that are not critical to protein function (pages 7-9). There is no guidance provided as to which amino acids can be added, deleted or substituted and the polypeptide would retain its biological function. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of the polypeptide determines its structural and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar activity/utility requires a knowledge with regard to which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expected intolerant to modification) and detailed knowledge of the ways in which the polypeptide's structure relates to function. However, the problem of the prediction of polypeptide structure from mere sequence data of a single polypeptide and in turn utilizing predicted structural determinations to ascertain functional aspects of the polypeptide and finally what

changes can be tolerated with respect thereto is extremely complex and outside of the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen multiple substitutions or multiple modifications of other types and the positions within the polypeptide's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any polypeptide and the result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modifications, e.g., multiple substitutions. The sequence of some polypeptides is highly conserved and one skilled in the art would not expect tolerance to any amino acid modification in such polypeptides.

Factors to be considered in determining whether undue experimentation is required, are set forth in In re Wands 8 USPQ2d 1400. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Applying the above test to the facts of record, it is determined that 1) no declaration under 37 C.F.R. 1.132 or other relevant evidence has been made of record establishing the amount of experimentation necessary, 2) insufficient direction or guidance is presented in the specification with respect to selecting other antigens having claimed functional features, 3) the relative skill of those in the art is commonly recognized as quite high (post-doctoral level). One of skill in the art would require guidance, in order to make or use polypeptides that are variants of SEQ ID NO: 2 in a manner reasonable in correlation with the scope of the claims. Without proper guidance, the experimentation is undue.

Applicant urges that the specification teaches that one skilled in the art certainly could design, make and test phenotypically silent and conservative variants of SEQ ID NO:2. Applicant urges that it is routine to make amino acid substitutions of a bout 20 amino acid polypeptides and to test the resulting variants for specific binding to an anti-*Ehrlichia* antibody. Applicant urges that the test of enablement is not merely quantitative since a considerable amount of experimentation is permissible, if it is merely routine or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

Applicant urges that the specification teaches that making and testing the polypeptides and variants of the invention are trivial as outlined in the specification. Applicant urges that a reasonable expectation of success is not a standard for enablement. Applicant urges that one in the art would expect to identify the claimed variants using only routine experimentation.

Applicant's arguments filed February 23, 2004 have been fully considered but they are not persuasive. It is the Examiner's position that Applicant has not shown enablement for variants of SEQ ID No.2. The specification discloses only species SEQ ID NO: 2 within the genus of the claimed invention. The specification proposes to discover other members of the genus by using a sequence comparison algorithm (pages 6-7). The specification also states " that naturally occurring variants and non-naturally occurring variants are included in the invention and may be produced by mutagenesis techniques or by direct synthesis" (page 7). The specification discloses only SEQ ID No:2 which corresponds to an isolated protein of *Ehrlichia.* The specification fails to provide guidance as to which amino acids can be changed and the polypeptides still retain their claimed biological function. The nature of the species within a genus are variant structures. In the present state of the art, the structure of a limited number of species does not provide guidance to the structure of others and is insufficient to support the claimed invention. To address Applicant's comment regarding "a reasonable expectation of success is not required under 35 U.S.C. 112, first paragraph", it should be noted that the 35 U.S.C. 112 first paragraph requires that Applicants teach how to "make and use" the claimed invention not how to "find" variants

of SEQ ID NO:2 that specifically bind to an anti-*Ehrlichia* antibody". A structural description is required. One skilled in the art would require guidance in order to make and use the claimed composition of matter or article of manufacture comprising phenotypically silent amino acid substitution variants of SEQ ID NO:2 commensurate in scope with the claims. Therefore, one skilled in the art would have to be successful in producing polypeptides that are variants of SEQ ID NO:2 which have a defined structure to satisfy the enablement requirement under 35 U.S.C. 112, first paragraph.

6. The rejection under 35 U.S.C. 102(a) is maintained for claims 1-9 and newly submitted claims 10-13 for the reasons set forth on pages 9-11, paragraph 5 of the previous Office Action.

The rejection was on the grounds that Rikihisa et al teach immunogenic compositions comprising the isolated polypeptide of SEQ ID NO:2 and pharmaceutically acceptable adjuvants (page 12). Rikihisa et al teach an antigen (i.e. isolated polypeptide) used in a Western immunoblot analysis and a dot blot analysis to detect the presence of antibody to *E. canis* ( page 17). The polypeptide of SEQ ID No: 2 is disclosed in Figure 19A). The article of manufacture (i.e. dot blot used in the dot blot analysis) would be inherent in the teachings of the prior art. It is well known in the art to include packing material that comprises a label to indicate the intended use of the article of manufacture. The composition and article of manufacture of Rikihisa, et al appears to be the same as the claimed invention.

Since the Office does not have the facilities for examining and comparing applicant's composition and article of manufacture with the composition and article of manufacture of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the composition and article of manufacture of the prior art does not possess the same material structural and functional characteristics of the claimed composition and article of manufacture). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant urges that under 102, a claim is anticipated only if each and every element as set forth in the claim is found in a single art reference. Applicant urges that a certain characteristic may occur or be present in a prior art reference is not sufficient to establish inherency of that characteristic. Applicant urges that the Office has not provided a basis in fact and/or technical reasoning to show that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. Applicant urges that Rikihisa et al do no teach or suggest the used of polypeptide fragments in devices an in particular do not teach or suggest the particular fragment shown in SEQID NO:2. Applicant urges that the Office has not provided basis that the whole recombinant protein antigens in Rikihisa et al would be fragmented in any way. Applicant urges that the claimed compositions of matter provide greater sensitivity than the reagents taught in Rikihisa et al (see the declaration of Dr. Chandrashekar).

Applicant's arguments filed February 23, 2004 have been fully considered but they are not persuasive. It is the Examiner's position that there is nothing on the record to show that the claimed composition and article of manufacture differs from the composition and article of manufacture of the prior art. The claims are drawn to composition and article of manufacture consisting essentially of an isolated polypeptide shown in SEQ ID NO:2 or a phenotypically silent amino acid substitution variant thereof. Rikihisa et al teach an antigen (i.e. isolated polypeptide) used in a Western immunoblot analysis and a dot blot analysis to detect the presence of antibody to *E. canis* ( page 17). The claimed invention encompass variants of SEQ ID NO: 2, therefore one skilled in the art could reasonably conclude that the *E. canis* polypeptides

of the prior art are variants of SEQ ID NO:2 since Rikihisa et al teach that the invention embraces non-naturally occurring allelic forms or derivatives of the outer membrane proteins (i.e. P30) (page 10) and Rikihisa et al claim isolated polypeptides that are at least 85% homologous to the amino acid sequence shown in Figure 19 (claim 20, page 19). It should noted that the polypeptide of SEQ ID No: 2 is disclosed in Figure 19B (amino acid residues 61-79) and represents a polypeptide that is at least 85% homologous to the amino acid sequence shown in Figure 19. Applicant has provided no side-by-side comparison to show that the claimed polypeptide differs from the *E. canis* polypeptides of the prior art. It should be noted that the claim recites "consisting essentially of" which is open claim language which suggest that other components that do not cause a negative effect on the compositions of matter can be present in the claimed invention.

In regards to Applicant's referral to the Declaration filled under 37 C.F.R. 1.132 (declaration of Dr. Chandrashekar) to point out that the compositions of matter of the claimed invention are more sensitive than that of the prior art, it should be noted that there are not limitations in the claims requiring that the compositions of matter require any particular level sensitivity. To address Applicant's comments regarding inherency, there is no limitation in the claims nor is this issue addressed in the Examiner's rejection. The prior art teaches composition and article of manufacture consisting essentially of a phenotypically silent amino acid substitution variants of SEQ ID NO:2. Therefore, Rikihisa et al anticipate the claimed invention.

7. The rejection under 35 U.S.C. 112, second paragraph is maintained for claims 1-9 and newly submitted claims 10-13 for the reasons set forth on page 12, paragraph 7 of the previous Office Action.

The rejection was on the grounds that claims 1-9 are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1-9 are indefinite because the claims recite "phenotypically silent substitutions variants". It is unclear as to what the Applicant is referring?

Applicant urges that one of skill in the art would know the meaning of phenotypically silent amino acid substitution variants given in the specification. Applicant urges that Bowie et al, *Science* 247:1306-1310 (1990) and the specification page 7, lines 14-17 provides guidance concerning how to make phenotypically silent amino acid substitutions.

Applicant's arguments filed February 23, 2004 have been fully considered but they are not persuasive. It is the Examiner' s position that metes and bounds of "phenotypically silent amino acid substitutions" cannot be ascertained by what is disclosed in the instant specification. The specification and Bowie et al merely teaches that amino acids modifications can be made. It should be noted that Bowie et al discloses that problems exist with the prediction structure and function from a sequence (page 1).

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (571) 272-0857. The examiner can normally be reached on Monday – Friday from 9:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (571) 272–0864.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov./>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vanessa L. Ford
Biotechnology Patent Examiner
May 6, 2004

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